



Time-course of depressive symptoms in patients with heart failure

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ABSTRACT

Background: It is unclear how depressive symptoms in patients with heart failure develop over time and whether this trajectory of depressive symptoms is associated with hospital admission and prognosis.

Aim: To describe the time-course of depressive symptoms and determine the relationship with hospitalisation and mortality.

Method: Data was analysed using 611 patients with completed CES-D questionnaires at baseline and at 18 months. Data on hospitalisation was collected 18 months after discharge and data on mortality was collected 18 and 36 months post-discharge.

Results: A total of 140 (61%) of the 229 patients with depressive symptoms at discharge had recovered from depressive symptoms after 18 months whereas 71 (18%) of the 382 non-depressed developed depressive symptoms and 89 (39%) of the 229 depressed remained depressed. Patients with recently (i.e. during the last 18 months) developed depressive symptoms showed a significantly higher risk for cardiovascular hospitalisation (HR 1.7, 95% CI 1.1–2.6, $P = .016$). After 36 months, patients with developed depressive symptoms after discharge were at a higher risk of all-cause mortality (HR 2.0, 95% CI 1.2–3.5, $P = .012$) and there was a trend towards a higher risk of all-cause mortality in patients with ongoing depressive symptoms (HR 1.7, 95% CI 0.98–3.1, $P = .056$).

Conclusion: A significant proportion of patients with HF, who were reported depressive symptoms at discharge recovered from depressive symptoms during the following 18 months. However, patients who remained having depressive symptoms or patients who developed depressive symptoms had a worse prognosis.

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Introduction

Heart failure (HF) is a clinical syndrome that is increasing in incidence worldwide. It results in high morbidity and mortality, and a lower five year survival rate than many common forms of cancer such as breast and prostate cancer [1]. Major depression and depressive symptoms are common in patients with HF and significantly more frequent compared to an age and gender matched population [2]. It is estimated that 16%–38% of patients with HF have depressive symptoms, depending on the type of assessment diagnostic instruments used [3]. The presence of depressive symptoms, even in the absence of a confirmed diagnosis of major depressive disorder, increases the risk of non-compliance [4,5], delay in seeking hospital care [6], higher usage of health care resources and clinical events [7,8]. In addition, the presence of depression may also affect the impact of disease management

programs, as these interventions may not be as effective in depressed patients [9].

Despite these adverse outcomes of depression in HF patients, only a few trials have been published that address treatment and the results are inconclusive [10,11]. In the large scaled SADHART-CHF study ($n = 469$), treatment with selective serotonin re-uptake inhibitor (SSRI) was not favourable compared to placebo regarding reductions in depressive symptoms as well as in long-term follow-up end points [10]. In a small pilot study ($n = 36$), however, SSRI improved depressive symptoms and general health perceptions, compared with placebo [11].

Others have shown that changes in depressive symptoms are associated to poorer outcomes. In patients with HF ($n = 147$) an increase in Beck Depression Inventory score (BDI) from baseline to 1-year follow-up was associated with an increased number of cardiovascular hospitalisations and deaths over a median of 5 years follow-up from baseline [12]. Blumenthal and colleagues, in their study of effects of exercise training on depressive symptoms, had the same experience and reported that a decrease in BDI score between baseline and

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3-month follow-up was associated with an increased number of hospitalisations and deaths [13]. However these studies did not report on the proportions of patients whose depression remitted, or those that, stayed depressed or developed depression. From the ENRICH study (a study in post MI patients), it is known that a large proportion of depressed patients remit spontaneously, without any structured intervention [14]. The same experience has been reported in HF patients [15,16]. In the study of Fulop and colleagues, patients with depressive symptoms at 24 weeks (persistent or recently developed) also used significantly more health care resources compared to those without depressive symptoms [15]. In the study of Dekker and colleagues, patients with persistent or incident depressive symptoms at 3 or 6 months had the worst health-related quality of life [16]. With the exception of these two studies [15,16] it is today unclear how depressive symptoms in HF patients develop over time and how this trajectory of depressive symptoms is associated with hospital admission and prognosis. Such information could help in the interpretation of the effect of depressive symptoms on clinical events and might also guide optimal timing of assessment for depressive symptoms in HF.

The purpose of this study was to describe the time-course of depressive symptoms in patients with HF during 18 months following hospitalisation due to HF and determine its relationship with the hospital admission rate and mortality. A second purpose was to compare the prognostic information of depressive symptoms assessed 18 months after hospital discharge.

Methods

Study design

Data was collected in the COACH (Coordinating study evaluating Outcomes of Advising and Counselling in Heart failure) study and additional long-term follow-up data was collected. COACH was a multi-centre, randomised trial designed to compare basic and intensive support to standard treatment in patients with HF. The methodology, main results and baseline depression data of the trial have been published previously [17–19]. In summary, patients were recruited during a period of 28 months from October 2002 to February 2005. All patients had been admitted to hospital with symptoms of HF, New York Heart Association (NYHA) functional classification II–IV. Patients were > 18 years of age and had evidence of structural underlying heart disease. Major exclusion criteria were: concurrent inclusion in another study or in a HF clinic, inability to complete the questionnaires; any invasive procedure or cardiac surgery intervention within

the last 6 months or planned during the following 3 months; ongoing evaluation for heart transplantation; and inability or unwillingness to give informed consent. After written informed consent, patients were randomised into three groups: care as usual and two intervention groups (basic and intensive support). Patients completed questionnaires and were interviewed by an independent interviewer not involved in the care for these patients. The Central Ethics Committee approved the study, including the 3-year extended follow-up, and the investigation conformed to the principles outlined in the Declaration of Helsinki.

Measurements

Depressive symptoms

Depressive symptoms were assessed by The Centre for Epidemiological Studies Depression Scale (CES-D). This questionnaire was administered a few days before discharge from the hospital and 18 months after hospitalisation. The CES-D is a 20-item self-report questionnaire designed to measure depressive symptoms in the general population and in the medically ill [20]. A total sum score is used (0–60), with higher scores indicating more depressive symptoms. A cut-off point of 16, which is generally used to define patients at risk of clinical depression was used to distinguish between HF patients with depressive symptoms (CES-D \geq 16) and patients without depressive symptoms (CES-D < 16). By using baseline and 18-month data, patients were classified into 4 categories of depressive symptoms: 1) ongoing: patients with depressive symptoms at index hospitalisation and at the 18-month follow-up; 2) remission: patients with depressive symptoms at index hospitalisation but not at 18-month follow-up; 3) new episode: patients without depressive symptoms at index hospitalisation but with depressive symptoms at 18-month follow-up and 4) non depressed: patients without depressive symptoms at index hospitalisation and 18-month follow-up.

Hospitalisation and mortality

Data on hospitalisation and mortality was collected from the patient's medical record and by interviews with the patient during follow-up. In this study, data on hospitalisation was collected 18 months after discharge whereas data on mortality was collected at 18 and 36 months after discharge. Hospitalisation was defined as an unplanned overnight stay in a hospital due to any cause. Regarding the 18-month follow-up period, reason for hospitalisation, cause of death and date of the event were adjudicated by a central end-point committee. Concerning the 36-month (1095 days) follow-up, only data on mortality was collected from the hospital registry, the patient's general practitioner and/or the municipality.

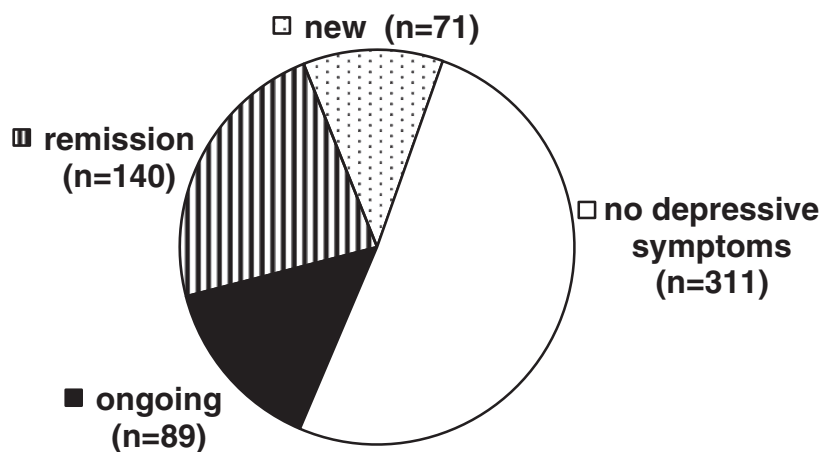


Fig. 1. Course of depressive symptoms in HF patients during the 18-month follow-up. (n = 611).

Demographic and clinical data

Demographic and clinical variables known from the literature, to be potentially important prognostic factors in the relation between the course of depressive symptoms and adverse events in HF patients were identified. Demographic factors included age, sex, and living situation and were assessed by patient interview during index hospitalisation. Clinical factors included primary reason for HF, the presence of comorbidity (e.g. asthma/COPD, diabetes, rheumatoid arthritis, renal disease, stroke and hypertension), disease severity (B-type Natriuretic Peptide-BNP) and history of HF hospitalisation, which were collected from medical records and by patient interview.

Statistical analysis

The prevalence of depressive symptoms was calculated at baseline and 18 months after discharge. Bivariate analyses were conducted to compare demographic and clinical characteristics at baseline among the 4 depressive symptom status groups (ongoing depression, recovered depression, new depressive episode, and persistent non-depressed). Outcomes, days to first hospitalisation and mortality were compared among the different categories of depressive symptom status by chi-square tests for categorical data and by non-parametric tests (Kruskal–Wallis) for continuous variables. Multivariable proportional hazard regression models were used to evaluate the independent association between depressive symptom status and the risk of hospital admissions and mortality. Firstly we evaluated the change in CES-D score over the 18 months follow-up period (CES-D score at 18 months minus baseline CES-D score). Secondly, to facilitate communication and summarisation of findings we also evaluated the 4 depressive symptom status groups (ongoing, recovered, new episode, non-depressed). Kaplan–Meier curve analyses were performed to investigate the association between depression symptom status groups and hospitalisation after 18 months and mortality 36 months after hospital discharge. The multivariate analyses were adjusted for demographics age, sex, chronic obstructive pulmonary disease, diabetes, ischemic HF, baseline BNP level, and history of history of HF hospitalisation because of their known influence on outcome and/or because they differed significantly by depression status ($P < .05$). In the continuous analysis we also adjusted for baseline CES-D score. In the analysis of the risk of hospitalisation, a previous history of HF hospitalisation (yes or no format) was one or more events prior to inclusion in the study, whereas in the 36 months mortality analysis. A previous history of HF hospitalisation refers to one or more events during the 18-month follow-period. In the present study data on all patients in the COACH study was analysed as one rather than three intervention groups, since the presence of depressive symptoms was equally distributed among the intervention groups at baseline and the intervention was not associated with readmission or mortality. SPSS 18.0 (IBM, SPSS, Chicago, IL) was used for statistical analyses.

Results

Study sample

A total of 1023 patients with HF were enrolled in the COACH study and 958 and 649 patients completed the CES-D at baseline and after 18 months respectively. Analyses were performed on the 611 patients with a complete CES-D score at baseline as well as at 18-month follow-up. The main reason for missing CES-D data at the 18-month follow-up was mortality ($n = 271$). Those who did not complete the CES-D at follow-up ($n = 412$) were significantly older, had more comorbidity, and a higher mean baseline CES-D score.

Prevalence and time-course of depressive symptoms

Of the 611 HF patients, 229 (38%) reported depressive symptoms (CES-D ≥ 16) at index hospitalisation. Eighteen months after discharge, 160 (26%) of the 611 patients reported depressive symptoms. In total, 61% ($n = 140$) of the 229 HF patients who were depressed during the index hospitalisation remitted from depressive symptoms (CES-D < 16) whereas 39% ($n = 89$) still had a CES-D score ≥ 16 (ongoing depressive

symptoms) at 18 months post-discharge. Out of the 382 patients without depressive symptoms at index hospitalisation, 81% ($n = 311$) remained without depressive symptoms whereas 19% ($n = 71$) had developed depressive symptoms at 18 months follow-up (Fig. 1). Patients with ongoing depressive symptoms or with a new episode of depressive symptoms were more likely to have diabetes, COPD and a history of previous HF hospitalisations compared to those who recovered from depression. Patients who recovered from depression had higher BNP levels at hospital discharge, but there was no difference in prescription of antidepressants (Table 1).

Outcomes

Association between the trajectory of depression and hospitalisation 18 months after discharge

The multivariate proportional hazard regression analyses showed that an increase in depression symptoms as indicated by a higher CES-D score (1 point CES-D change) over an 18-month interval, after adjustments (i.e. age, sex, baseline CES-D score, COPD, diabetes, ischemic HF, baseline BNP level and history of HF hospitalisation previous inclusion in the study) was significantly associated with a small increased risk of hospitalisation because of cardiovascular reasons (HF included) (HR 1.02 CI 95% 1.01–1.04, $P = .003$) and of all-cause hospitalisation (HR 1.02 CI 95% 1.01–1.04, $P = .003$) but not of hospitalisation due to HF (HR 1.02 CI 95% 0.99–1.04, $P = .07$). Patients with depressive symptoms at 18 months (i.e. ongoing or recently developed) were more often readmitted during the 18-month of follow-up compared to patients without or who recovered from depressive symptoms (61% and 61% vs. 44% and 47% respectively, $P < .01$) (Table 2). More patients with ongoing or recently developed depressive symptoms were hospitalized related to HF only, or for cardiovascular reasons (HF included) ($P = .03$ and $P = .01$ respectively) (Table 2). However, in multivariate proportional hazard regression analyses (adjusted for age, sex, BNP level, COPD, diabetes, ischemic HF, history of HF hospitalisations), only patients with recently developed depressive symptoms showed a significantly higher risk of all-cause hospitalisation (HR 1.5, 95% CI 1.03–2.2, $P = .035$) and CV hospitalisation (HR 1.7, 95% CI 1.1–2.6, $P = .016$), but not of HF hospitalisation (HR 1.4, 95% CI 0.8–2.7, $P = .21$).

Association between depression status, the trajectory of depression and all-cause mortality 36 months after discharge

Of the patients with depressive symptoms at the follow-up 18 months after discharge, the follow-up analysis 18 months after that re-assessment (i.e. 36 months after hospital discharge) showed that 26% of the depressed patients had died, compared to 15% among non-depressed patients (Log rank $P = .001$; Fig. 2). The 18-month change in CES-D scores after adjustments (i.e. age, sex, baseline CES-D score, COPD, diabetes, ischemic HF, baseline BNP level and history of HF hospitalisation during the 18 months follow-up) was significantly associated with a higher 36-month mortality (HR 1.04 CI 95% 1.02–1.06, $P < .001$). Unadjusted Kaplan Meier curves showed significant differences in all-cause mortality at the 36-month follow-up regarding depressive symptom status (Log rank $P = .008$; Fig. 3). A total of 25% of patients with ongoing depression and 28% of patients with recently developed depression had died and 15% and 16% of patients who remitted or were non-depressed had died at the 36-month follow-up (Table 2). In the multivariate proportional hazard regression analyses (i.e. age, sex, COPD, diabetes, ischemic HF, baseline BNP level and previous HF readmission) patients with recently developed depressive symptoms were at significantly higher risk of all-cause mortality (HR 2.0, 95% CI 1.2–3.5, $P = .012$). In patients with ongoing depression, there was only a trend towards a higher risk for all-cause mortality (HR 1.7, 95% CI 0.98–3.1, $P = .056$).

Discussion

To our knowledge, this is one of the first studies to investigate the time-course of depressive symptoms in HF patients and the relationship with hospitalisation and mortality. It was found that 61% of patients with depressive symptoms had recovered 18 months after hospitalisation, whereas 19% of those without depressive symptoms had developed depressive symptoms. Increase in depressive symptoms from hospitalisation to 18 months follow-up provided prognostic information. Patients with recently developed depressive symptoms were at a particularly higher risk of both hospitalisation and mortality.

From initial assessment of depressive symptoms during hospitalisation to re-assessment 18 months later, the occurrence of depressive symptoms decreased from 38% to 26%. Almost the same figures were described in the study by Fulop and colleagues who described that depressive symptoms in HF patients decreased from 36% at hospital to 26% 24 weeks post-discharge [15]. We found that 61% of patients who were depressed during hospitalisation had remitted in 18 months without significant antidepressant treatment. A recent sub-analysis of data from the SADHART-trial showed that 68% of those in the placebo group remitted from depression after the 14 week study period [21]. The present study, all patients received follow-up with different levels of intensity

Table 1
Baseline characteristics and differences according to depressive symptoms status

	All patients (n = 611)	Ongoing depressive symptoms (n = 89)	Remission depressive symptoms (n = 140)	New episode depressive symptoms (n = 71)	No depressive symptoms (n = 311)	P value
Demographic variables						
Age, y	69 ± 11	69 ± 11	68 ± 13	70 ± 13	69 ± 11	0.79
Female sex	38%	43%	49% ^{3,4}	34%	33%	0.004
Living alone	36%	48% ^{3,4}	37%	29%	33%	0.04
Clinical variables						
BNP pg/ml (median,IQR) ^a	370 (170–792)	369 (176–813)	494 ³ (213–1045)	293 (147–803)	365 (155–610)	<0.041
Co-morbidity						
COPD	27%	45% ^{2,3,4}	25%	28%	23%	<0.001
Diabetes	24%	27%	19%	35% ^{2,4}	23%	0.06
Ischemic aetiology	40%	35%	31%	45% ²	44% ²	0.03
History of HF hospitalisations ^a	27%	34%	21%	30%	27%	0.21
Medication						
ACE/ARB	85%	79% ⁴	85%	82%	88%	0.10
Beta blocker	68%	63%	70%	65%	69%	0.65
Diuretics	96%	96%	94%	97%	96%	0.79
Anti depressants	6%	11% ⁴	8%	7%	4%	0.09
Support						
Care as usual	32%	37%	31%	31%	32%	0.78
Basic intervention	34%	33%	34%	34%	34%	
Intensive intervention	34%	30%	35%	35%	34%	

Note: ACE-I/ARB – angiotensin converting inhibitor/angiotensin receptor blockers; BNP – brain natriuretic peptide; COPD – chronic pulmonary disease; HF – heart failure; IQR – inter quartile range;

¹ ongoing depressive symptoms; ² remission depressive symptoms; ³ new episode depressive symptoms; ⁴ no depressive symptoms.

^a Hospitalisation due to heart failure previous inclusion in the study.

[18], either by nurses or cardiologists. In the SADHART-CHF study both treatment and placebo groups were supported by nurses throughout the study period [10]. The high rates of remissions in the present study and in SADHART-CHF may therefore not be generalised to an ordinary HF population. However, in the study by Fulop et al. in which HF patients did not receive any specific structured follow-ups, 47% and 71% had remitted from depressive symptoms 4 and 24 weeks post-discharge [15]. High rates of remission was also reported in a recent study of the trajectory of depressive symptoms in HF, in which 50% of the patients experienced improvements by 3 to 6 months [16].

One explanation for remission is that depression and HF to some extent share the same somatic symptoms (i.e. fatigue, sleep disturbances and loss of appetite). Additionally, we found higher BNP levels at discharge in those who had remitted from depressive symptoms at follow-up. It is therefore plausible that some of the remitting patients might have been falsely labelled as depressed. Another possible explanation for the high hospitalisation rate is that depressive symptoms during hospitalisation may reflect a reactive depression. After discharge a HF stabilisation and improvements in patients physical and emotional status can be expected [22], which may influence remission of depression.

Table 2
Depressive symptom status and outcome after 18 months and all-cause mortality at the 3-year follow-up

Outcome	Ongoing depressive symptoms (n = 89)	Remission depressive symptoms (n = 140)	New episode of depressive symptoms (n = 71)	No depressive symptoms (n = 311)	P value
Hospitalisation 18 months					
HF hospitalisation	27%	15%	25%	16%	0.03
CV hospitalisation (incl. HF)	43%	32%	49%	31%	0.01
All-cause hospitalisation	61%	47%	61%	44%	0.01
All-cause mortality 3-year follow-up					
	25%	16%	28%	15%	0.01

Note: CV – cardiovascular; HF – heart failure.

Regression to the mean could be another potential additional explanation for the reduction in depressive symptoms.

The results of the present study also showed that a change in depressive symptoms from discharge from hospital to 18-months follow-up provided prognostic information. In particular it was those patients who had developed depression who was at a significantly higher risk whereas those with ongoing depression were at borderline risk predictive of a poorer outcome. Blumenthal and colleagues reported that in patients who had undergone coronary artery by-pass surgery (CABG) those with a CES-D score ≥ 16 at discharge and 6-months later, had an increased mortality, whereas those with remitting or newly developed depression had not [23]. However, the HR for the CABG patients with newly developed depression was much the same as that for ongoing

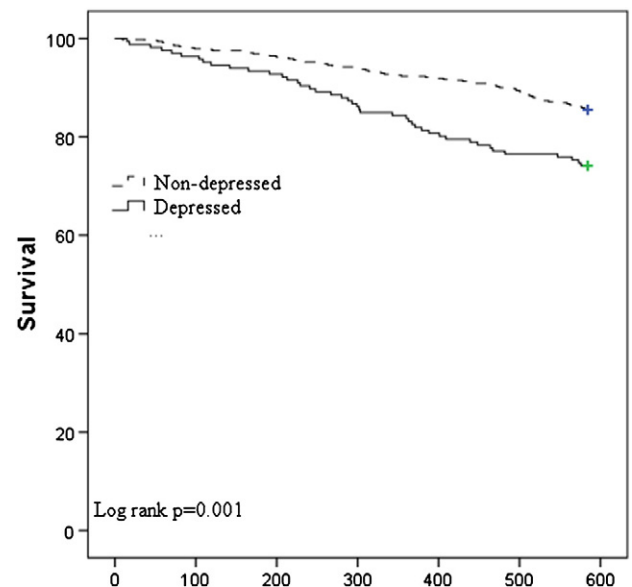


Fig. 2. Unadjusted Kaplan Meier curve of depression symptoms status re-assessed 18 months after discharge and all-cause mortality after 18 months (i.e. three years post-discharge).

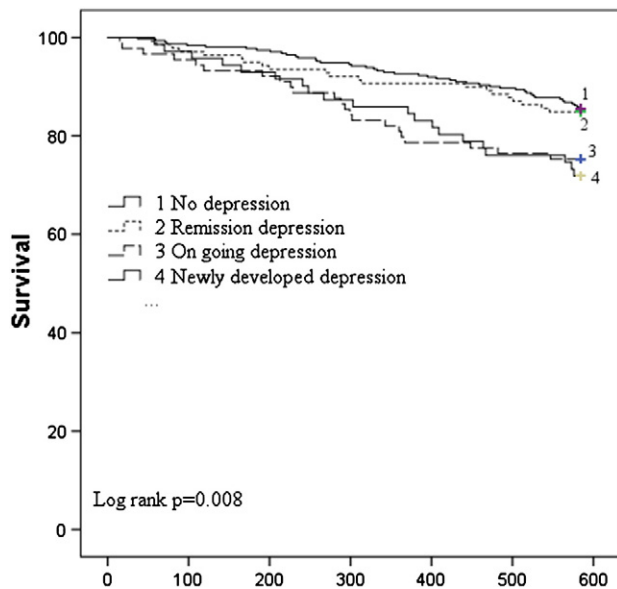


Fig. 3. Unadjusted Kaplan Meier curve of the depression symptoms status 18 months after discharge and all-cause mortality after 18 months (i.e. three years post-discharge).

depression, and the lack of significance may be explained by a small number of patients in the latter group ($n = 36$). Another study by the COACH study group had previously shown that baseline CES-D > 24, and not CES-D score of ≥ 16 was associated with poor outcomes [8]. This is in line with Blumenthal et al. who suggested that a baseline score on the CES-D of ≥ 27 , or a CES-D ≥ 16 at baseline and 6 months, may identify patients with clinical depression [23]. A sub-study of the SADHART trial described that non-remission was more common in HF patients who at baseline were assessed to have severe depression, and that those who did not remit had a worse prognosis [24]. This suggests that mild depressive symptoms are not predictive for poor outcomes. HF patients screened to have depressive symptoms during a hospitalisation compared to those found in outpatient care are more likely to experience remission from depressive symptoms 3 to 6 months post-discharge [16]. This and to avoid adverse medical side-effects one may suggest no to initiate treatment of depression during hospitalisation for HF, but to wait at least one month post-discharge, until patients have stabilised [15]. Therefore patients with severe depression could have a follow-up visit to re-evaluate depressive symptoms and a possible treatment strategy. In our study, patients who developed depression after discharge from the hospital were at the highest risk of re-hospitalisation or mortality. These results confirm other studies that describe that outpatients with HF, who report an ongoing or worsening of depressive symptoms are at higher risk for decline in health-related quality of life [16], physical functioning [25], cardiovascular hospitalisations or death [12]. It was also found that patients with ongoing depression had a borderline significant risk of death (HR 1.7, 95% CI 0.98–3.1, $P = .056$). Studies in non HF populations have shown that almost one-third of patients with remitted depression will have a recurrence of depression [26]. Assessing the psychological status of patients regularly, instead of only once in an outpatient setting or primary care setting, may therefore be an important strategy to identify HF patients who remain chronically depressed or who develop depression. However, before implementation of routine screening of depressive symptoms into clinical practice, establishment of treatment programs for approaching depressive symptoms in patients with HF and other cardiac diseases are needed [27].

It is important to note that this study was not primarily designed to follow the trajectory and describe the natural history of depression in patients with HF. The time interval of 18 months and the fact that there were only two measurement points of depression leads the possibility that patients with cyclic states such as those with several

remission and recurrence periods, may go undetected. The questionnaire CES-D is a valid and frequently used instrument; however, it is limited by the fact that it cannot be used to diagnose depression. Despite that we controlled for several important variables such as baseline BNP and history of HF hospitalisations, is it possible that the associations between poor outcomes and newly developed depression could reflect worsening of HF. Future studies exploring the trajectory of depression in HF patients should screen for depression using both questionnaires and diagnostic tools suggestively four times during at least one year. Today there is a lack of knowledge about the trajectory of depression in HF patients and we therefore think that this study, despite its limitations, is of interest.

In summary, this study found that 61% of the patients' depressive symptoms recovered spontaneously at 18 months following hospitalisation for HF. Patients who had depressive symptoms 18 months after discharge from hospital were found to have a worse prognosis. Those with a recently developed depression were at a particularly high risk of hospital readmission or death. Routine assessments of HF patients in primary care or at outpatient clinics in order to identify recently developed or chronic depressions may increase quality of life and decrease the risk for adverse outcomes in heart failure patients.

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